

Current Diagnosis and Management of Myocarditis

Windhi Dwijanarko, Hasanah Mumpuni, Bambang Irawan

Department of Cardiology and Vascular Medicine
Faculty of Medicine Universitas Gadjah Mada - Dr. Sardjito General Hospital, Yogyakarta, Indonesia

ABSTRACT

Myocarditis is an inflammation of the myocardium. The clinical presentations of myocarditis range from nonspecific systemic symptom such as fever, myalgias, palpitations, or exertional dyspnea, to severe hemodynamic derangement and sudden death. The wide variation of clinical manifestations has made the exact incidence of myocarditis difficult to determine. The prevalence of myocarditis based on autopsy data is ranging from 2 to 42%. Myocarditis has heterogeneous clinical presentation, ranging from mild chest pain or palpitations to cardiogenic shock and life-threatening ventricular arrhythmias. The diagnosis of myocarditis requires a high initial suspicion. Non-invasive techniques, such as cardiac magnetic resonance imaging, can be useful to diagnose and monitor of disease. The endomyocardial biopsy is the gold standard for definitive diagnosis of myocarditis and can identify the etiology of myocarditis. By endomyocardial biopsy, it can direct patients who can be managed by conventional therapy or who require specific treatment based on underlying etiology, such as antiviral or intravenous immunoglobulin infusion.

Keywords: myocarditis; diagnosis; management

Introduction

Myocarditis is an inflammation of the myocardium. The clinical presentations of myocarditis range from nonspecific systemic symptom such as fever, myalgias, palpitations, or exertional dyspnea, to severe hemodynamic derangement and sudden death. The wide variation of clinical manifestations has made the exact incidence of myocarditis difficult to determine. The use of endomyocardial biopsy has helped to understand the natural history of myocarditis and to clarify the clinicopathological correlations.¹

The prevalence of myocarditis based on autopsy data is ranging from 2 to 42%.² In biopsy-proven myocarditis, the prevalence is ranging between 9 and 16% of adult patients suffering from idiopathic non-ischaemic dilated cardiomyopathy (DCM). In most patients with mild symptoms and minimal left ventricular dysfunction, myocarditis subside spontaneously without specific treatment. However, about 30% of cases, in biopsy-proven myocarditis can

progress to DCM and have a poor prognosis.² The aim of the review is to inform the current diagnosis and management of myocarditis.

Definition

Myocarditis refers to every inflammation in the myocardium. Inflammation can be occurred after any form of injury to the heart, including ischemia, mechanical trauma, and genetic cardiomyopathies. According to the Dallas criteria, acute myocarditis is defined by lymphocytic infiltrates in association with myocyte necrosis. Borderline myocarditis is defined as inflammatory infiltrates without evidence of myocyte necrosis.³ Newer histologic criteria rely on cell-specific immunoperoxidase stains for surface antigens such as anti-CD3, anti-CD4, anti-CD20, anti-CD28, and antihuman leukocyte antigen. The criteria based on this type of staining has greater sensitivity than the Dallas criteria and may have more prognostic value.⁴

In the 2007 European Society of Cardiology (ESC) classifications of cardiomyopathies

and the 2013 ESC myocarditis Task Force report, myocarditis is defined histologically as an inflammatory disease of the myocardium diagnosed by endomyocardial biopsy, based on histological, immunological, immunohistochemical and molecular findings to detect possible infectious causes.^{2,5,6} The term inflammatory cardiomyopathy may be used for

histologically confirmed myocarditis with cardiac dysfunction.⁷

Etiology

The etiology is large variety of infectious agents, systemic diseases, drugs, and toxins (table 1). Viral infections are the most important

Table 1. Causes of myocarditis classification

Type	Causes	Specific
1. Infectious myocarditis	Bacterial	<i>Staphylococcus</i> , <i>Streptococcus</i> , <i>Pneumococcus</i> , <i>Meningococcus</i> , <i>Gonococcus</i> , <i>Salmonella</i> , <i>Corynebacterium diphtheriae</i> , <i>Haemophilus influenzae</i> , <i>Mycobacterium</i> (tuberculosis), <i>Mycoplasma pneumoniae</i> , <i>Brucella</i>
	Viral	RNA viruses: Coxsackieviruses A and B, echoviruses, polioviruses, influenza A and B viruses, respiratory syncytial virus, mumps virus, measles virus, rubella virus, hepatitis C virus, dengue virus, yellow fever virus, Chikungunya virus, Junin virus, Lassa fever virus, rabies virus, human immunodeficiency virus-1 DNA viruses: adenoviruses, parvovirus B19, cytomegalovirus, human herpes virus-6, Epstein-Barr virus, varicella-zoster virus, herpes simplex virus, variola virus, vaccinia virus
	Spirochaetal	<i>Borrelia</i> (Lyme disease), <i>Leptospira</i> (Weil disease)
	Fungal	<i>Aspergillus</i> , <i>Actinomyces</i> , <i>Blastomyces</i> , <i>Candida</i> , <i>Coccidioides</i> , <i>Cryptococcus</i> , <i>Histoplasma</i> , <i>Mucor-mycoses</i> , <i>Nocardia</i> , <i>Sporothrix</i>
	Protozoal	<i>Trypanosoma cruzi</i> (Chagas disease), <i>Toxoplasma gondii</i> , <i>Entamoeba</i> , <i>Leishmania</i>
	Parasitic	<i>Trichinella spiralis</i> , <i>Echinococcus granulosus</i> , <i>Taenia solium</i> , <i>Schistosoma</i>
	Rickettsial	<i>Coxiella burnetii</i> (Q fever), <i>R. rickettsii</i> (Rocky Mountain spotted fever), <i>R. tsutsugamushi</i>
2. Immune-mediated myocarditis	Allergens	Tetanus toxoid, vaccines, serum sickness Drugs: penicillin, cefaclor, colchicine, furosemide, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, phenylbutazone, methyldopa, thiazide diuretics, amitriptyline
	Alloantigens	Heart transplant rejection
	Autoantigens	Infection-negative lymphocytic, infection-negative giant cell. Autoimmune disorders: systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Kawasaki's disease, inflammatory bowel disease, scleroderma, polymyositis, myasthenia gravis, insulin-dependent diabetes mellitus, thyrotoxicosis, sarcoidosis, Wegener's granulomatosis, rheumatic heart disease (rheumatic fever)
3. Toxic myocarditis	Drugs	Amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, hemetine, interleukin-2, trastuzumab, clozapine
	Heavy metals	Copper, iron, lead (rare, more commonly cause intramyocyte accumulation)
	Physical agents	Radiation, electric shock, hypothermia, heat stroke
	Hormones	Phaeochromocytoma, vitamins: beri-beri
	Miscellaneous	Scorpion sting, snake, and spider bites, bee and wasp stings, carbon monoxide, inhalants, phosphorus, arsenic, sodium azide

RNA, ribonucleic acid; DNA, deoxyribonucleic acid; HIV, human immunodeficiency virus; CMV, cytomegalovirus; EBV, Epstein-Barr Virus; HSV, herpes simplex virus (Source: Caforio et al., 2013)²

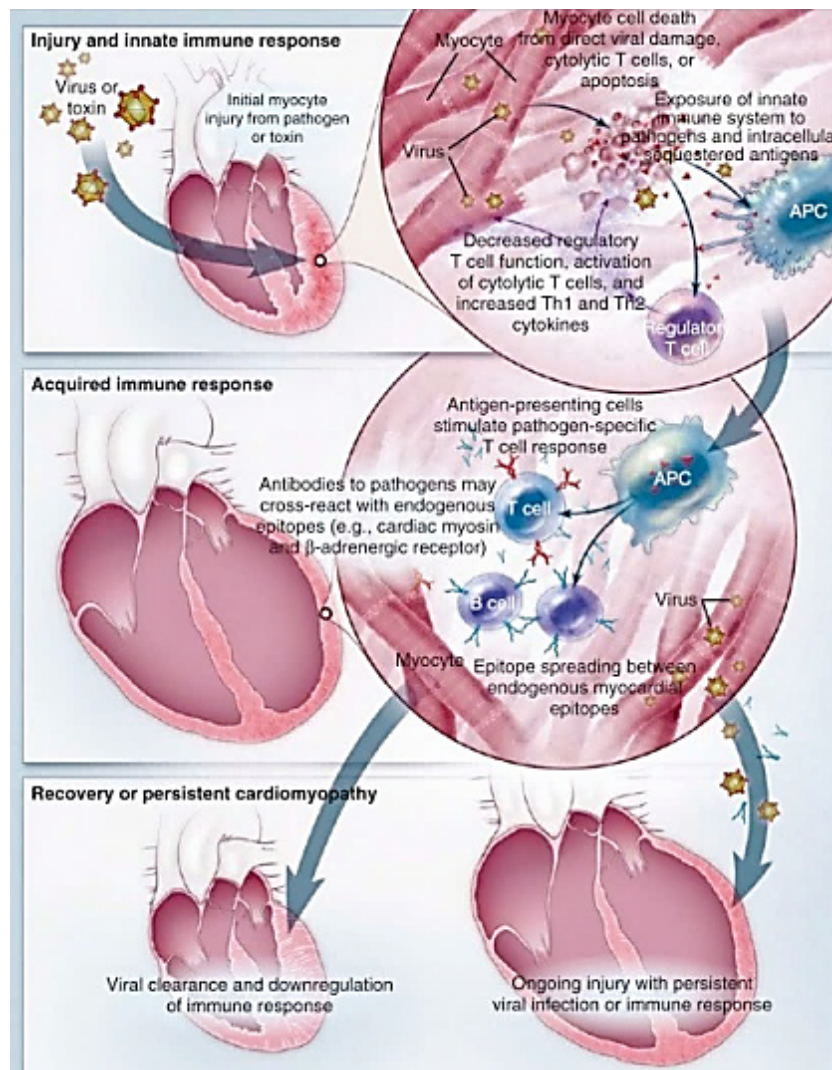


Figure 1. Pathogenesis process of myocarditis (Source: Cooper, 2009)¹¹

cause of myocarditis in North America and Europe with genomes of enterovirus, adenovirus, influenza viruses, human herpes virus-6 (HHV-6), Epstein-Barr-virus, cytomegalovirus, hepatitis C virus, and parvovirus B19 reported in the myocardium of patients with myocarditis and DCM.² In a multicenter study of 624 patients with biopsy-proven myocarditis (66%) or borderline myocarditis (34%), evidence of viral genome (adenovirus, enterovirus, and cytomegalovirus) was detected in 38% of subjects' endomyocardial biopsies.⁸ Human immunodeficiency virus (HIV) has been associated with cardiotropic

viral infection resulting in myocarditis and left ventricular dysfunction. It is often unclear clinically whether the HIV virus itself, medications used for treatment, or myocardial coinfection is responsible for the observed left ventricular systolic dysfunction due to myocarditis.⁹

In the myocarditis, if no viruses are identified in endomyocardial biopsy and other known causes are excluded, lymphocytic and giant cell myocarditis are presumed idiopathic or autoimmune. Similarly, the diagnosis of idiopathic granulomatous myocarditis (cardiac sarcoidosis) requires negative stains for microorganisms.

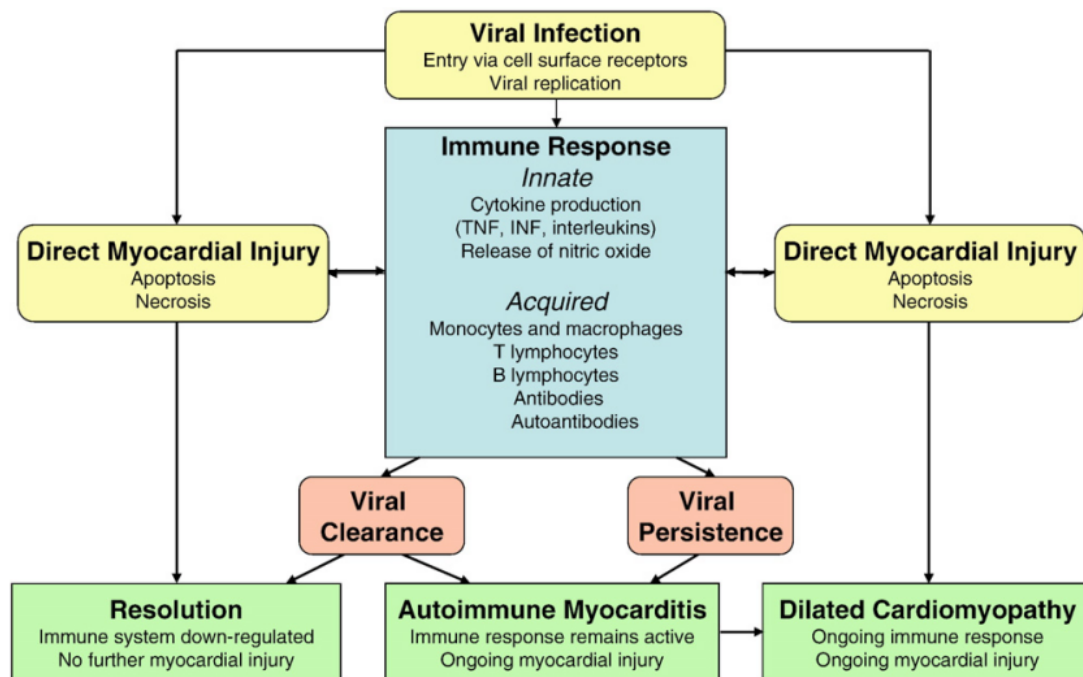


Figure 2. Pathogenesis of myocarditis (Source: Blauwet & Cooper, 2010)¹³

Autoimmune myocarditis can be exclusively cardiac involvement or as a part of autoimmune disorders with extra-cardiac manifestations, such as in sarcoidosis, hypereosinophilic syndrome, scleroderma, and systemic lupus erythematosus. Autoimmune myocarditis is a primary antigen responsible for progression from a self-limited viral infection to subsequent autoimmune disease.¹⁰

The bacterial-induced myocarditis is far less common than viral-induced myocarditis. Toxin-producing bacteria, including clostridium and diphtheria, can cause severe myocardial damage. Bacteremia from any source may result in myocarditis. The most common is meningococcus, streptococcus, and *Listeria*. Regional wall-motion abnormalities or perfusion defects that are not in the distribution of a coronary artery may also be seen in noninfectious disorders, such as cardiac sarcoidosis and arrhythmogenic right ventricular cardiomyopathy or dysplasia.¹¹

Drug-induced hypersensitivity reactions and systemic hypereosinophilic syndromes can cause a specific myocarditis. Numerous medications, including some anticonvulsants,

antibiotics, and antipsychotics, have been associated with hypersensitivity myocarditis.¹² Eosinophilic myocarditis is characterized by a largely eosinophilic infiltrate in the myocardium. It may occur in association with systemic diseases, such as the hypereosinophilic syndrome, the Churg-Strauss syndrome, Löfller's endomyocardial fibrosis, cancer, and parasitic, helminthic, or protozoal infections.¹² Clinical manifestations of eosinophilic myocarditis include congestive heart failure, endocardial and valvular fibrosis, and endocardial thrombi. A rare disorder, acute necrotizing eosinophilic myocarditis is a progressive form of eosinophilic myocarditis with an acute onset and a high fatality rate.¹²

Other substances other than infectious agents can affect on the heart and injure the myocardium. In some cases, the damage is acute, transient, and associated with evidence of an inflammatory myocardial infiltrate with myocyte necrosis. Other agents that harm the myocardium can lead to chronic changes with resulting histologic evidence of fibrosis and a clinical picture of a dilated or restrictive

cardiomyopathy.¹³ Radiation therapy can lead to a variety of cardiac complications that arise long after the completion of radiation therapy, including pericarditis with effusion, tamponade, or constriction; coronary artery fibrosis and myocardial infarction; valvular abnormalities; myocardial fibrosis; and conduction disturbances. Radiation-induced cardiac damage is related to the cumulative dose of the radiation, and the mass of heart irradiated.¹³

Pathogenesis

The pathogenesis of viral myocarditis can be divided into three major components: viral infection and replication, immunologic response (innate and

adaptive immune response), and phase of cardiac remodeling or recovery¹⁴ (figure 1).

Viruses enter the host through a variety of locations including the gastrointestinal system or the respiratory system. The virus binds to a viral receptor, ultimately resulting in internalization of the virus. This process includes entry of the viral capsid proteins and the viral genome. The virus may undergo initial replication in the host in organs such as the liver, spleen and pancreas. Ultimately, the virus reaches the heart via dissemination through the blood or lymphatic vessels.¹³

After viral entry acute injury of the myocytes, induced by virus replication leads to myocyte necrosis, exposure of intracellular antigens (e.g.

Table 2. Clinical Presentations of Patients with Inflammatory Heart Muscle Disease

- 1. Acute coronary syndrome-like**
 - (a) Acute chest pain
 - Frequently starting within 1–4 weeks of a respiratory or gastrointestinal infection
 - Frequently associated with severe and recurrent symptoms
 - In the absence of angiographic evidence of CAD
 - (b) ST/T wave changes
 - ST-segment elevation or depression
 - T-wave inversions
 - (c) With or without normal global or regional LV and/or RV dysfunction on echocardiography or CMR
 - (d) With or without increased TnT/TnI that may have a time course similar to acute myocardial infarction or a prolonged and sustained release over several weeks or months
- 2. New onset or worsening heart failure in the absence of CAD and known causes of heart failure**
 - (a) New onset or progressive heart failure over 2 weeks to 3 months
 - Dyspnoea
 - Peripheral oedema
 - Chest discomfort
 - Fatigue
 - (b) Impaired systolic LV and/or RV function, with or without an increase in wall thickness, with or without dilated LV and/or RV on echocardiography or CMR
 - (c) Symptoms possibly started after a respiratory or gastrointestinal infection, or in the peri-partum period
 - (d) Non-specific ECG signs, bundle branch block, AV-block, and/or ventricular arrhythmias
- 3. Chronic heart failure in the absence of CAD and known causes of heart failure**
 - (a) Heart failure symptoms (with recurrent exacerbations) of >3 months duration
 - (b) Fatigue, palpitation, dyspnoea, atypical chest pain, arrhythmia in an ambulant patient
 - (c) Impaired systolic LV and/or RV function on echocardiography or CMR suggestive of DCM or non-ischaemic cardiomyopathy
 - (d) Non-specific ECG signs, sometimes bundle branch block and/or ventricular arrhythmias and/or AV-block
- 4. 'life-threatening condition', in the absence of CAD and known causes of heart failure comprising**
 - (a) Life-threatening arrhythmias and aborted sudden death
 - (b) Cardiogenic shock
 - (c) Severely impaired LV function

(Source: Caforio et al., 2013)²

cardiac myosin), and activation of the host's immune system, which is characterized by the invasion of natural killer cells and macrophages followed by T lymphocytes. The acute phase of myocarditis takes only a few days. After the acute phase of virus-induced injury, the second phase is characterized by immune reactions. Cytokine activation and antibodies to viral and cardiac proteins may worsen cardiac damage and cause injury of the contractile function. The balance of immune response by the host is a major determinant of patient outcome.¹⁵ The first host responses to the viral are the innate immune system. Activation of acquired immunity can lead to the production of T-killer cells that can directly damage the virus and virally infected cells. The activation of T cells also leads to the activation of B cells and the production of specific antibodies to neutralise the antigen. This response results in subacute and chronic inflammation in myocarditis and contributes to the subsequent myocyte necrosis, fibrosis, and remodelling.¹⁶

If the inflammatory response persists, the heart can endure remodelling. It is a modification of the cardiac structure and function, which leads to the development of dilated cardiomyopathy (figure 2). The inflammatory process from both innate and acquired immunity can lead to release of cytokines, which are potent activators of matrix

metalloproteinases that can digest the interstitial collagen and elastin in the heart. The final result is dilated cardiomyopathy, with systolic and diastolic dysfunction, and progressive heart failure.¹³

Clinical Presentation

Myocarditis clinical presentation is ranging from mild symptoms, such as chest pain and palpitations to life-threatening cardiogenic shock and ventricular arrhythmia. The disease may affect individuals of all ages, with most frequently occurring in the young.² This diversity of clinical presentation implicates that the diagnosis of myocarditis requires a high level of suspicion early in the course of the disease. In all cases of suspected myocarditis, it is mandatory to exclude coronary artery disease and other cardiovascular disease that could explain the clinical presentation. If this is strongly suspected by the clinician, further investigation including endomyocardial biopsy may be proper diagnostic tool.²

Myocarditis should be suspected in a previously asymptomatic young subject with few coronary artery disease risk factors who, days or weeks after a supposed respiratory or gastrointestinal viral syndrome, develops dyspnoea or orthopnoea, or palpitations, or effort intolerance/malaise, or heart failure, or

Table 3. Diagnostic criteria for clinically suspected myocarditis

I. ECG/Holter/stress test features	
Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia	
II. Myocardiocytolysis markers	
Elevated Troponin T/I	
III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)	
New, otherwise unexplained LV and/ or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi	
IV. Tissue characterization by CMR	
Oedema and/or LGE of classical myocarditic pattern	

(Source: Caforio *et al.*, 2013)²

chest pain (which may be pleuritic if concomitant pericarditis present) with or without cardiac troponin I or T (cTNI or cTNT) release and unobstructed coronary arteries at coronary angiography.¹⁷ The clinical manifestation of myocarditis varies ranging from asymptomatic course to presentations with signs of myocardial infarction to devastating illness with cardiogenic shock. Chest pain, cardiac arrhythmias, and acute or chronic heart failure can occur during the course of the disease.¹⁸

Diagnosis

Non-invasive imaging techniques such as cardiac magnetic resonance (CMR) imaging can be useful in making the diagnosis of myocarditis and for monitoring disease progression. However, endomyocardial biopsy is the gold standard for the diagnosis of definite myocarditis. In order to improve recognition of myocarditis in clinical practice and to aid selection of patients that require further diagnostic evaluation and treatment, the working group proposed new criteria for clinically suspected myocarditis for which biopsy analysis is recommended (table 3).

Myocarditis should be suspected in the presence of²:

- 1 or more of the clinical presentations in table 3, with or without ancillary features
- 1 or more of the diagnostic criteria from different categories (I to IV) in table 3
- when the patient is asymptomatic, 2 or more diagnostic criteria from different categories (I to IV)

Ancillary features which support the clinical suspicion of myocarditis include:

- fever $\geq 38^{\circ}\text{C}$ at presentation or within the preceding 30 days with or without evidence of a respiratory (chills, headache, muscle aches, general malaise) or gastrointestinal (decreased appetite, nausea, vomiting, diarrhoea) infection

- peri-partum period
- previous clinically suspected or definite myocarditis (according to the criteria set in Table 3)
- personal and/ or family history of allergic asthma, other types of allergy, extra-cardiac autoimmune disease, toxic agents
- family history of DCM, myocarditis (according to the present criteria).

These criteria are based upon consensus of experts. The hospital that can not perform endomyocardial biopsy or do not have access to state-of-the-art CMR should refer patients with clinically suspected myocarditis to a tertiary referral unit experienced in endomyocardial biopsy and CMR, particularly when patients present with haemodynamic instability or life-threatening arrhythmia. In patients fulfilling the diagnostic criteria for clinically suspected myocarditis, it is recommended to selective coronary angiography and endomyocardial biopsy. This recommendation also applies to patients with an acute coronary syndrome-like presentation.²

The Electrocardiography Examination

The electrocardiogram (ECG) is widely used as a screening tool despite low sensitivity. The ECG findings in patients with myocarditis vary from non specific T-wave and ST-segment changes mimicking an acute myocardial infarction. It includes ST-segment elevation in ≥ 2 contiguous leads (54%), T-wave inversions (27%), widespread ST-segment depressions (18%), and pathological Q waves (18% to 27%). Atrial or ventricular conduction defect, supraventricular and ventricular arrhythmias can occur in patients with myocarditis. The presence of Q waves or a new left bundle branch block are associated with higher rates of cardiac death or heart transplantation.¹ A QTc prolongation >440 ms, abnormal QRS axis, and ventricular ectopic beats are associated with poor clinical outcome.

A prolonged QRS duration of >120 ms is an independent predictor for cardiac death or heart transplantation. Hence, the ECG represents an easily available tool for risk stratification in patients with suspected myocarditis.¹⁵

The Echocardiography Examination

Echocardiography helps to rule out non-inflammatory cardiac disease such as valve disease and to monitor changes in cardiac chamber size, wall thickness, ventricular function, pericardial effusions and the presence of intracavitary thrombi. Global ventricular dysfunction, regional wall motion abnormalities, and diastolic dysfunction with preserved ejection fraction may occur in myocarditis. Myocarditis may be similar to dilated, hypertrophic, and restrictive cardiomyopathy. It may also mimic ischaemic heart disease. Fulminant myocarditis often presents with a non-dilated, thickened, and hypocontractile left ventricle, because of severe inflammatory response results in interstitial oedema and loss of ventricular contractility.²

Pericardial effusions suggestive of myopericarditis may also be observed and help to make a diagnosis. Diastolic filling patterns are abnormal in most patients, with a restrictive pattern frequently present. Right ventricular dysfunction may present in only the minority of patients. Segmental wall motion abnormalities may be observed in more than half of patients, which included hypokinetic, akinetic, or dyskinetic regional pattern. Reversible left ventricular hypertrophy is observed in a few patients and typically resolved over several months. Thus, echocardiographic findings can be varied but relatively nonspecific.¹

The Biomarker Examination

The biomarker for myocarditis is non specific. Cardiac troponins are highly suggestive of acute myocarditis, when other potential causes of myocardial necrosis have

been excluded. NT-pro-BNP or BNP levels should be measured when heart failure is suspected, but normal values do not exclude myocarditis. Newer cardiac biomarkers, such as copeptin or midregional pro- adrenomedullin, do not provide additional diagnostic or prognostic information. Nonspecific markers of inflammation (white blood cellcount, C-reactive protein, and erythrocyte sedimentation rate) are often elevated in myocarditis.¹⁹ Positive viral serology does not imply myocardial infection but rather indicates the interaction of the immune system with an infectious agent. Antibodies of IgG class, which are shown to be cardiac and disease-specific for myocarditis, can be used as autoimmune biomarkers for identifying at risk relatives and those patients in whom, in the absence of active infection of the myocardium, immunosuppression and/or immunomodulation may be beneficial.²

The endomyocardial biopsy

The gold standard in diagnosis of myocarditis is still the endomyocardial biopsy. Endomyocardial biopsy confirms the diagnosis of myocarditis and identifies the underlying aetiology and the type of inflammation (e.g. giant cell, eosinophilic myocarditis, sarcoidosis). It imply different treatments and prognosis. If endomyocardial biopsy is performed by experienced teams, the complication rate is very low (0–0,8%).¹⁵

The 2007 American Heart Association/ American College of Cardiology Foundation/ European Society of Cardiology scientific statement on endomyocardial biopsy limited its class I recommendations to unexplained new-onset heart failure of less than 2 weeks duration associated with hemodynamic compromise or unexplained new-onset heart failure of 2 weeks to 3 months duration associated with a dilated left ventricle and new ventricular arrhythmias or conduction disturbances.⁶ However, in a recent position statement from the 2013 European Society of Cardiology, the recommendation for

endomyocardial biopsy is extended, including patients with a pseudo-infarct presentation after exclusion of coronary artery disease.²

The complications of endomyocardial biopsy include hematoma, arteriovenous fistula, vasovagal reaction, pneumothorax, arrhythmia, heart block, infection, tricuspid valve damage, pulmonary embolism or systemic embolism during left ventricular biopsy, and cardiac chamber perforation with possible hemopericardium and cardiac tamponade.²⁰ Left ventricular biopsy has also been proven to be a safe procedure. The complications is only occurred in 0.33 % of patients who underwent left ventricular endomyocardial biopsy.²¹

The Imaging Examination

Cardiovascular magnetic resonance (CMR) imaging provides non-invasive tissue characterization of the myocardium and can support the diagnosis of myocarditis. The timing of CMR in suspected myocarditis will depend upon local availability and expertise, but it is reasonable to first perform CMR in clinically stable patients, prior to endomyocardial biopsy.

CMR findings are consistent with myocardial inflammation, if at least two of the following criteria are present:

- 1) Regional or global myocardial signal intensity increase in T2-weighted oedema images
- 2) Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images
- 3) There is at least one focal lesion with non-ischaemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (late gadolinium enhancement)

When at least criteria are met, a sensitivity of 76% and specificity of 96% have been reported in patients with clinically suspected acute myocarditis and pseudoinfarction presentation. A repeat CMR study between 1 and 2 weeks after the initial CMR study is recommended if:

- a) None of the criteria are present, but the onset of symptoms has been very recent and there is strong clinical evidence for myocardial inflammation

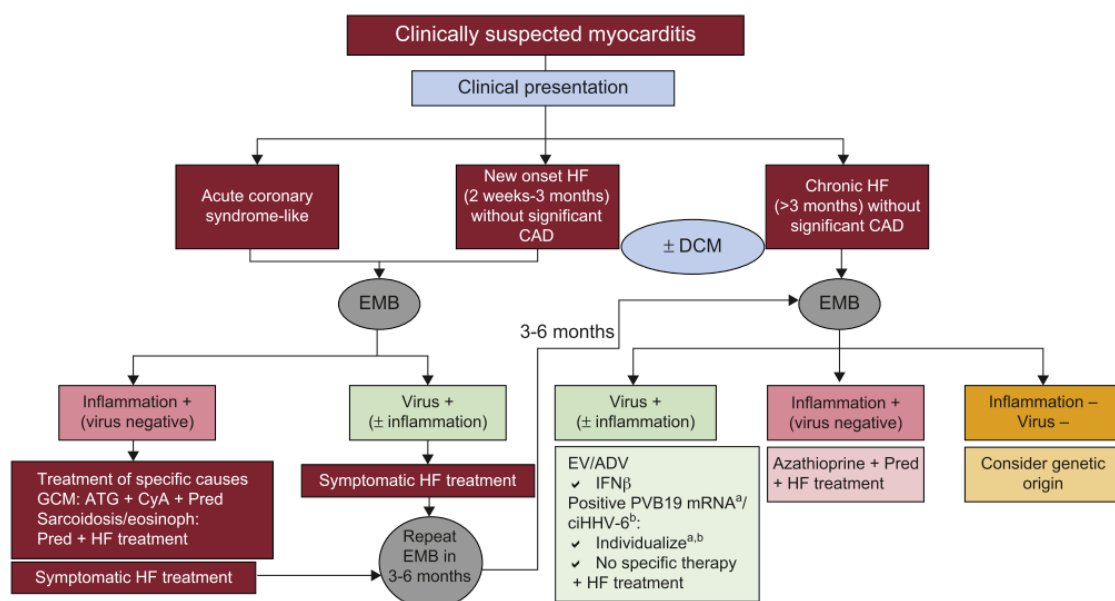


Figure 3. Myocarditis treatment according to clinical setting and endomyocardial biopsy results (Source: Dominguez et al., 2016)¹⁹

- b) One of the criteria is present
The presence of left ventricle dysfunction or pericardial effusion provides additional, supportive evidence for myocarditis.²

Recent studies have shown good correlations between CMR results and endomyocardial biopsy in acute myocarditis. However, obtaining the biopsy from the region of late gadolinium enhancement of the CMR has not proven to increase the yield of diagnosis and in chronic myocarditis, the diagnostic performance of CMR was found to be worse (sensitivity 63%; specificity 40%).¹⁵ Therefore, CMR might not be appropriate to guide clinical management in chronic myocarditis. The detailed information about the degree of inflammation, the presence of special forms of myocarditis (e.g., giant cell or eosinophilic myocarditis, which require specific therapies), or the presence and type of virus is not available in CMR.¹⁵

MANAGEMENT

Outcome and prognosis of myocarditis depends on aetiology, clinical presentation and disease stage. Acute myocarditis resolves in about 50% of cases in the first 2–4 weeks, but about 25% will develop persistent cardiac dysfunction and 12–25% may acutely deteriorate and fatal or progress to end-stage dilated cardiomyopathy. Biventricular dysfunction at presentation has been reported as the main predictor of death or transplantation. Fulminant myocarditis of unknown aetiology is more frequent in children and far less in adults.²

Conventional Medical Treatment

Patients with haemodynamically unstable heart failure should be cared promptly according to current ESC guidelines for heart failure in intensive care units with respiratory and mechanical cardio-pulmonary support facilities.²² In acute/fulminant cases with cardiogenic shock

and severe ventricular dysfunction, ventricular assist devices or extracorporeal membrane oxygenation (ECMO) may be needed to provide a bridge to transplant or to recovery. Because of its simplicity and effectiveness, ECMO therapy can be salvaged this group of patients.²²

When myocarditis is suspected in asymptomatic or mildly symptomatic patients, admission to the hospital and clinical monitoring are recommended until a definite diagnosis is established. The need for monitoring is mandatory, since the clinical condition can evolve rapidly and a cardiopulmonary emergency (e.g. severe heart block or life-threatening arrhythmia) is threatening and unpredictable. Exercise testing is contraindicated in the acute stage as it can precipitate arrhythmia.¹⁹ Patients with haemodynamically stable heart failure should be treated with diuretics, angiotensin-converting enzyme inhibitor, or angiotensin receptor blockade and beta-adrenergic blockade.¹⁹ In patients who have persistent heart failure symptoms in spite of optimal management, additional treatment with aldosterone antagonists should be considered. The procedure for weaning of heart failure therapy following recovery of ventricular function is not clearly defined. The use of non-steroidal anti-inflammatory drugs, in particular acetylsalicylic acid, are a cornerstone of treatment for acute pericarditis, but have been associated with increased mortality in experimental models of myocarditis.^{2,19}

There are no specific recommendations for the management of arrhythmia in myocarditis, and so management should be in line with current ESC guidelines. Sinus bradycardia, prolonged QRS duration, increased left ventricular hypokinesis on echocardiography, may precede a life-threatening arrhythmia.² Temporary pacing may be needed for complete atrio-ventricular block. Indication for cardioverter defibrillator implantation (ICD) is controversial, because myocarditis may resolve completely.¹⁹

Physical activity should be restricted during the acute phase of myocarditis until the disease has completely resolved. After resolution of the clinical presentation (at least 6 months after the onset of the disease), clinical reassessment is indicated before resumes competitive activity for athletes and non-athletes.²

Specific Medical Treatments

Autoimmune/ Virus Negative

In some patients, inflammation persists, despite viral clearance. In these patients, the inflammatory process is due to a post-infectious state or autoimmunity. Some randomized trials have shown that immunosuppressive therapy in these patients is superior to conventional treatment alone in terms of LV ejection fraction and NYHA classification improvement.²³ In the TIMIC study,²³ chronic myocarditis virus-negative patients with less than 45% LV ejection fraction who received conventional heart failure for at least 6 months were randomized to placebo vs cortisone and azathioprine. The LV ejection fraction improved in 89% of patients from the treatment group and in none in the placebo group. Furthermore, a previous study observed that only virus-negative patients improve with immunosuppression.²³

Viral Cardiomyopathy

There is still no approved antiviral-therapy for the treatment of viral myocarditis. Treatment with acyclovir, gancyclovir, and valacyclovir may be considered in patients with herpes virus infection, although their efficacy is unproven in myocarditis.² Preliminary data on interferon-beta (IFN- β) treatment suggest that it eliminates enteroviral and adenoviral genomes in patients with left ventricular dysfunction, is associated with improvement in NYHA functional class and specifically in enteroviral infection, with a better 10-year prognosis.²

Among patients with chronic enteroviral or adenoviral cardiomyopathy, viral clearance

with a 6-month course of IFN- β therapy was accompanied by LV ejection fraction improvement and a significant decrease of ventricular dimensions in non-randomized trial.²⁴ The patients who cleared the virus spontaneously had higher levels of endogenous IFN- β than those with viral presently persist.²⁴ Thus, these findings support the efficacy of IFN- β therapy.¹⁹

High dose intravenous immunoglobulin (IVIG) modulates the immune and inflammatory response by a variety of mechanisms and is used in a number of systemic autoimmune diseases. Its use has been associated with improved LV ejection fraction in chronic symptomatic heart failure of various causes, but IVIG was ineffective in the recent-onset dilated cardiomyopathy in which only 15% of patients had biopsy-proven myocarditis of non-specified cause.² IVIG may be used in myocarditis refractory to conventional heart failure therapy, both viral and autoimmune forms, particularly if autoantibody-mediated.²

Prognosis

Myocarditis patients can have partial or full clinical recovery; some may relapse many years after the first episode. Relapses should be managed similarly to the previous myocarditis episode. In patients who do not resolve, disease may continue subclinically and lead to dilated cardiomyopathy. The myocarditis patient with pseudo-infarct presentation, normal coronary arteries, and preserved ventricular function may be safely discharged when cardiac enzymes have come into the normal range, and should be long-term followed-up. In the event of prolonged (weeks or even months) documented increase of cardiac enzymes, and/or progressive reduction in left and/or right ventricular function, the patient should be readmitted to hospital to perform endomyocardial biopsy.²

Conclusion

Myocarditis is an inflammation of the heart muscle that can be found after the injury either because of exposure to external antigens, such as viruses, bacteria, parasites, toxins, or drugs, as well as internal boosters such as autoimmune activation. Myocarditis has heterogeneous clinical presentation, ranging from mild chest pain or palpitations to cardiogenic shock and life-threatening ventricular arrhythmias. The diagnosis of myocarditis requires a high initial suspicion. Non-invasive techniques, such as CMR, can be useful to diagnose and monitor of disease. The endomyocardial biopsy is the gold standard for definitive diagnosis of myocarditis and can identify the etiology of myocarditis. By endomyocardial biopsy, it can direct patients who can be managed by conventional therapy or who require specific treatment based on underlying etiology, such as antiviral or IVIG.

References

1. Magnani JW, Dec GW. 2006. Myocarditis: current trends in diagnosis and treatment. *Circulation*. 113(6):876-890.
2. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. 2013. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 34(33):2636-2648.
3. Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ, Jr., et al. 1987. Myocarditis. A histopathologic definition and classification. *Am J Cardiovasc Pathol*. 1(1):3-14.
4. Baughman KL. 2006. Diagnosis of myocarditis: death of Dallas criteria. *Circulation*. 113(4):593-595.
5. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, et al. 1996. Report of the 1995 World Health Organization/ International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. *Circulation*. 93(5):841-842.
6. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. 2008. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 29(2):270-276.
7. Leone O, Veinot JP, Angelini A, Baandrup UT, Basso C, Berry G, et al. 2012. 2011 consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. *Cardiovasc Pathol*. 21(4):245-274.
8. Bowles NE, Ni J, Kearney DL, Pauschinger M, Schultheiss HP, McCarthy R, et al. 2003. Detection of viruses in myocardial tissues by polymerase chain reaction. evidence of adenovirus as a common cause of myocarditis in children and adults. *J Am Coll Cardiol*. 42(3):466-472.
9. Barbaro G, Di Lorenzo G, Grisorio B, Barbarini G. 1998. Incidence of dilated cardiomyopathy and detection of HIV in myocardial cells of HIV-positive patients. Gruppo Italiano per lo Studio Cardiologico dei Pazienti Affetti da AIDS. *N Engl J Med*. 339(16):1093-1099.
10. Rose NR. 2009. Myocarditis: infection versus autoimmunity. *J Clin Immunol*. 29(6):730-737.
11. Cooper LT, Jr. 2009. Myocarditis. *N Engl J Med*. 360(15):1526-1538.
12. Corradi D, Vaglio A, Maestri R, Legname V, Leonardi G, Bartoloni G, et al. 2004. Eosinophilic myocarditis in a patient with

- idiopathic hypereosinophilic syndrome: insights into mechanisms of myocardial cell death. *Hum Pathol.* 35(9):1160-1163.
13. Blauwet LA, Cooper LT. 2010. Myocarditis. *Prog in Cardiovasc Dis.* 52(4):274-288.
14. Bonow R, Mann D, Zipes D, Libby P. 2012. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.* Ninth ed. Philadelphia: Elsevier Saunders. pp.1589-1602
15. Kindermann I, Barth C, Mahfoud F, Ukena C, Lenski M, Yilmaz A, et al. 2012. Update on myocarditis. *J Am Coll Cardiol.* 59(9):779-792.
16. Sagar S, Liu PP, Cooper LT, Jr. 2012. Myocarditis. *The Lancet.* 379(9817):738-747.
17. Caforio AL, Marcolongo R, Basso C, Iliceto S. 2015. Clinical presentation and diagnosis of myocarditis. *Heart.* 101(16):1332-1344.
18. Canter CE, Simpson KP. 2014. Diagnosis and treatment of myocarditis in children in the current era. *Circulation.* 129(1):115-128.
19. Dominguez F, Kühl U, Pieske B, Garcia-Pavia P, Tschöpe C. 2016. Update on Myocarditis and Inflammatory Cardiomyopathy: Reemergence of Endomyocardial Biopsy. *Revista Española de Cardiología (English Edition).* 69(02):178-187.
20. Holzmann M, Nicko A, Kuhl U, Noutsias M, Poller W, Hoffmann W, et al. 2008. Complication rate of right ventricular endomyocardial biopsy via the femoral approach: a retrospective and prospective study analyzing 3048 diagnostic procedures over an 11-year period. *Circulation.* 118(17):1722-1728.
21. Chimenti C, Frustaci A. 2013. Contribution and risks of left ventricular endomyocardial biopsy in patients with cardiomyopathies: a retrospective study over a 28-year period. *Circulation.* 128(14):1531-1541.
22. Mirabel M, Luyt CE, Leprince P, Trouillet JL, Leger P, Pavie A, et al. 2011. Outcomes, long-term quality of life, and psychologic assessment of fulminant myocarditis patients rescued by mechanical circulatory support. *Crit Care Med.* 39(5):1029-1035.
23. Frustaci A, Russo MA, Chimenti C. 2009. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. *Eur Heart J.* 30(16):1995-2002.
24. Kühl U, Lassner D, von Schlippenbach J, Poller W, Schultheiss HP. 2012. Interferon-beta improves survival in enterovirus-associated cardiomyopathy. *J Am Col Cardiol.* 60(14):1295-1296.